REMARKS

Claims 34-38 and 40-45 are pending in the application and claims 1-33 and 39 have been canceled.

In the January 30, 2008, Office Action, claims 34-38 and 40-45 were rejected under 35 U.S.C. § 103(a) as being obvious over Krebber and Mersmann further in view of Pluckthun "Producing antibodies in Escherichia coli: from PCR to fermentation" in ANTIBODY ENGINEERING (1996). The specific grounds for rejection, and applicants' response thereto, are set forth in detail below.

Rejections Under 35 U.S.C. §103(a)

Claims 34-38 and 40-43 are rejected under 35 U.S.C. §103 as obvious over Krebber and Mersmann, further in view of Pluckthun. Specifically, the Examiner states that Krebber teaches nucleic acids encoding a gene III N-terminal protein linked to a 10 amino acid purification tag where the nucleic acid lacks a signal sequence for exporting the encoded protein to the bacterial periplasm, and also asserts that Krebber teaches fusion proteins containing the bacterial protein β-lactamase. The Examiner also states that a peptide that lacks a signal sequence will inherently accumulate in an inclusion body in the bacterial cell. The Examiner further asserts that Krebber describes solubilization and purification of proteins from inclusion bodies.

Mersmann is cited as teaching phage display of antibody fusion proteins containing a signal sequence where the antibody sequence falls within the length limitations specified in the instant claims and is derived from a eukaryotic organism. Pluckthun allegedly "provides an insight as to what motivates one of ordinary skill in the art to practice the method of Mersmann et al. in the method of Krebber et al. such that gIII P fusion protein will be expressed and accumulate in the inclusion body." The Examiner goes on to say that Pluckthun shows that "one of ordinary skill in the art knows that any successful antibody expression strategy needs to ensure that various domains of the immunoglobulins are properly stabilized with the crucial intramolecular disulphide bonds" and that "[a]ntibody inclusion bodies are not fundamentally different from any other inclusion bodies and thus, may guidelines from general inclusion body production can be followed." Applicants respectfully traverse the rejection for the reasons set forth below.

The claims of the present application are directed to a nucleic acid molecule encoding a fusion protein comprising the first N-terminal domain (N1) of the gene III protein of filamentous phage and a (poly)peptide which is encoded by a nucleic acid sequence comprised in a genomic DNA fragment or an expressed sequence tag (EST). The gene III fusion partner is derived from a eukaryotic cell and is 100-2000 base pairs in length. The fusion protein lacks a signal sequence for transport of the fusion protein to the bacterial periplasm. The fusion proteins are useful, for example, for identifying antibodies that bind to the intact protein encoded by the full-length gene corresponding to the genomic fragment or EST.

The rejection set forth by the Examiner, and the stated rationales for the rejection, demonstrate that the Examiner apparently fails to appreciate why one of ordinary skill in the art would not have been motivated by the cited references to make the instant invention. Indeed, the Examiner's analysis lacks any discussion of *why* one of ordinary skill in the art would have been motivated to make the claimed invention in the first place, notwithstanding the Examiner's effort to rely on Pluckthun to provide the missing motivation.

The entire focus of Krebber is directed to gene III fusions that contain a signal sequence, where the fusion protein is exported to the bacterial periplasm once produced. As the Examiner is aware, this type of construct is exactly the opposite of the present invention, where the construct lacks a signal sequence. The constructs in Figure 3c, specifically cited by the Examiner in the office action, all contain a signal sequence, as described at page 609, right hand column, of Krebber ("[i]n all constructs (Figure 3c) the Bla-gIIIp fusion proteins were transported to the periplasm by signal sequences of either PelB, OmpA or gIIIp.")

The Examiner correctly notes that Krebber also describes an instance of a nucleic acid encoding an N-terminal domain of gene III attached to a short 10-amino acid histidine tag ("His-tag") having the sequence SGCPHHHHH (see, Figure 3d), for purifying the gene III protein. This construct lacks a signal sequence and is relied upon by the Examiner for a suggestion to make gene III fusions that lack a signal sequence.

However, as the Examiner acknowledges, the His-tag does not meet the limitation of the instant claims of being either a genomic DNA fragment or an expressed sequence tag (EST), nor is it 100-2000 base pairs in length – rather, it is encoded by 30 base pairs of DNA. Moreover, this construct as essentially the exact opposite to the instant invention: Krebber uses the His-tag to purify the gene III domain – in other words, Krebber uses an affinity reagent (a nickel resin)

that specifically binds the gene III fusion protein partner to purify the gene III domain, whereas in the instant invention, the fusion protein partner typically is subsequently used to screen antibody libraries to *identify* a specific binding partner (an antibody) for the fusion protein partner. The Examiner has put the cart before the horse: Krebber uses a fusion protein partner for which an affinity agent (Ni- resin) is well known, whereas in the instant invention the fusion partner is one for which an affinity agent (an antibody) *has yet to be identified.* One of ordinary skill in the art reading Krebber would not have had any motivation to modify Krebber to replace the His-tag with a much longer peptide encoded by a genomic DNA fragment or an EST, since this would have been of no value in purifying the gene III fragment. Nothing in Krebber teaches or suggests using a fusion partner for the gene III protein that is longer than the short purification tag while simultaneously lacking a signal sequence. In sum, Krebber provides no motivation whatsoever to one skilled in the art to prepare *any* construct encoding a gene III fragment and a genomic DNA fragment or EST, regardless of the length of the genomic fragment or EST

The Examiner cites Mersmann as teaching fusions with antibody fragments where those fragments are encoded by nucleic acid sequences having the length recited in the instant claims. However, once again the Examiner is combining apples and oranges: one of ordinary skill in the art would not have been motivated to combine the nucleic acid disclosed by Krebber, where the construct lacks a signal sequence, with the nucleic acid disclosed by Mersmann, where all the constructs contain a signal sequence.

The instant claims explicitly recite that the claimed nucleic acid molecule lacks a signal sequence for transport of the fusion protein to the bacterial periplasm. Mersmann provides no suggestion whatsoever to prepare a construct lacking a signal sequence – indeed, the opposite is true since Mersmann deals with classic display methodology where gene III fusion proteins are transported to the bacterial periplasm to combine with other phage proteins to make phage particles. Thus, one of ordinary skill in the art reading Mersmann would have been motivated to display fusion proteins *on the surface* of phage, rather than expressing the fusion protein in a manner that means that the proteins cannot reach the surface of the phage and instead accumulate *inside* the bacterial host. In this sense, Mersmann can be seen as teaching away from the instantly claimed invention by suggesting that gene III fusion proteins should contain a signal sequence and that the fusion protein should be displayed on the surface of a phage particle.

Pluckthun does nothing to cure the deficiencies of the primary references. The Examiner's comments about Pluckthun apparently reflect a lack of understanding regarding the nature of the instantly claimed invention. Thus, as stated in the instant specification, the fusion proteins encoded by the claimed nucleic acids are useful for, for example, screening antibody libraries, and particularly libraries of antibodies displayed on phage, for binders that will specifically recognize the fusion partner that is fused to the first N-terminal domain of the gene III protein. Thus, the claimed nucleic acids encode molecules that can be considered to be *antigens* for screening against phage antibody libraries.

By contrast, the Examiner's comments regarding Pluckthun focus on the refolding of antibodies produced in *E. coli* and formation of "crucial" disulfide bonds in those refolded antibodies. Applicants respectfully do not understand the significance of the Examiner's reference to antibody refolding or disulfide bond formation, and further point out that nothing in Pluckthun would have motivated one of ordinary skill in the art to have prepared the instantly claimed nucleic acids. Moreover, it is notable that the recombinant antibodies described by Pluckthun are not fusion proteins where the antibody is fused with the first N-terminal domain of the gene III protein. At most, Pluckthun can be taken as suggesting that proteins produced intracellularly in inclusion bodies can be solubilized and refolded. This is not, in itself, a controversial proposition. But it fails completely to provide the missing motivation that would have been required by one of ordinary skill in the art to prepare the instantly claimed nucleic acids. Thus, Pluckthun cannot provide any motivation to make the instantly claimed nucleic acids that encode fusion proteins when it fails to teach or suggest such fusion proteins.

In sum, Krebber deals mainly with fusion proteins that contain a signal sequence and, in the single instance where the fusion protein lacks a signal sequence, the fusion partner is merely a very short, artificial, affinity tag where the gene III protein is the protein of interest. Mersman deals only with phage antibody display where the fusion protein contains a signal sequence and provides no suggestion whatsoever that there would be any reason to remove the signal sequence – indeed, one of ordinary skill in the art would recognize that the presence of a signal sequence is absolutely key to the working of the methods described by Mersman. Pluckthun deals only with the practical aspects of expressing and refolding recombinant antibodies in *E. coli* and has nothing to do with making fusion proteins encoded by nucleic acids where genomic DNA fragments or ESTs are fused to the first N-terminal domain of the gene III protein.

The only suggestion to fuse genomic DNA fragments or ESTs to nucleic acid encoding the first N-terminal domain of the gene III protein of filamentous phage is found in the specification of the instant application. Even if the Examiner were correct that Mersmann, Krebber and Pluckthun somehow can be combined, the absence of any rationale for making the combination makes the instant rejection fatally flawed. Accordingly, withdrawal of the rejection respectfully is requested.

In addition, it is axiomatic that it is improper to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art. In the instant case, Krebber describes methods of making and using so-called "selectively infective" phage. In these methods, phages are made non-infective by replacing the first N-terminal domain of gIIIp with a ligand-binding protein. The ligand of interest is bound to the missing N-terminal domain, and when the ligand-binding domain on the phage surface binds to the ligand, then the phage is rendered infective by the N-terminal domain of gIIIp that is bound to the ligand. See the abstract and Figure 1c of Krebber. The filamentous phages which are used in Krebber are, therefore, completely *devoid* of N1-protein. One of ordinary skill in the art , reading Krebber *in its entirety*, would therefore be motivated to prepare nucleic acid fusions that *lack* the N1 domain of phage gene III, rather than, as is instantly claimed, that *contain* the N1 domain and a genomic DNA fragment or EST.

Moreover, as described above, prior to the present invention, there was no motivation in the art to prepare the DNA molecules as instantly claimed, where a gene encoding a potential antigenic fragment is fused to the N1 domain but lacks a signal sequence. However, the fusion proteins encoded by the claimed nucleic acids are particularly useful for screening phage antibody libraries for technical reasons that were not described, appreciated, or understood, prior to the present invention.

A major challenge of using phage display methods to screen libaries of binding molecules, such as antibodies, is to minimize non-specific adsorption of the phages in the binding procedure and, by so doing, increase the number of specific binders. This is particularly the case where (a) the selected target is uncharacterized or only poorly characterized, which is often the case with (poly)peptides encoded by an EST or by a genomic fragment, and (b) when *fusion* proteins have to be used, because fusion proteins always contain, besides the desired target

protein, at least one further unwanted part which will also serve as a potential target for some of the members of the binder library.

The present inventors have recognized that a recombinant library of antibodies displayed on the surface of a filamentous phage automatically removes individual phages which display Nl-binding immunoglobulins on their surface- in other words, no binders are found that bind to N1. This is presumably because the filamentous phage carry gene III on their surface which serves as a target for any N1-binding antibody, leaving them unavailable for binding elsewhere and eliminating those phage from the library. The Nl-containing fusion protein encoded by the instantly claimed nucleic acids is, therefore, surprisingly and unexpectedly effective for identifying specific binders for an unknown and/or uncharacterized (poly)peptide encoded by an EST or by a genomic fragment. See, for example, Example 1 on page 19 of the instant specification, which clearly demonstrates that a filamentous phage library surprisingly does not contain *any* Nl-binder (*"[i]n pannings Na and Nb, no binders against Nl were obtained...* ").

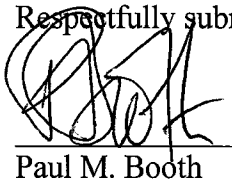
Prior to the recognition of this important effect by the present inventors there was no motivation in the art to make the instantly claimed nucleic acids which encode the first N-terminal domain of the gene III protein of filamentous phage fused to a (poly)peptide encoded by a genomic DNA fragment or an EST from a eukaryotic cell. In the absence of any such motivation, no *prima facie* case of obviousness exists, and withdrawal of the rejection respectfully is requested.

CONCLUSION

In view of the foregoing amendments and remarks, applicants respectfully submit that the application is in condition for allowance. Should the Examiner feel that there are any issues outstanding after consideration of this response, the Examiner is invited to contact the undersigned to expedite prosecution of the application.

The Commissioner is hereby authorized by this paper to charge any fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-3840. **This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).**

Respectfully submitted,



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